Appendix A

Version With Markings to Show Changes Made to Specification

Bold, Underlined Text indicates inserted text

Bracketed text indicates deleted text

In the Specification:

The paragraph beginning on Page 68, line 14:

Figure 26 shows a non limiting example of target signaling molecule inactivation of a zinzyme sensor molecule. In the absence of the target (SEQ ID NO. [31]**34**), the zinzyme sensor molecule (SEQ ID NO. [32]**35**) catalyzes the cleavage of a reporter molecule (SEQ ID NO. [33]**36**).

The paragraph beginning on Page 68, line 18:

Figure 27 shows a non-limiting example of target signaling molecule activation of a zinzyme sensor molecule. In the presence of the target (SEQ ID NO. [34]**37**), the zinzyme sensor molecule (SEQ ID NO. [35]**38**) catalyzes the cleavage of a reporter molecule (SEQ ID NO. [36]**39**).

The paragraph beginning on Page 68, line 12:

Figure 28 shows a non-limiting example of a nucleic acid sensor molecule that is modulated by a protein target signaling molecule, Erk. In the presence of the target protein (Erk), the nucleic acid sensor molecule (SEQ ID NO. [39]**41**) catalyzes the cleavage of a reporter molecule.

The paragraph on Page 68, line 26:

Figure 29 shows a non-limiting example of a "half-zinzyme" nucleic acid sensor molecule that is modulated by the 5'-UTR of the Hepatitis C virus (HCV 5'-UTR). The figure shows both inactive and active forms of the zinzyme sensor molecule (SEQ ID NO. [42]**43**). In the presence of the target signaling oligonucleotide (SEQ ID NO. [43]**26**) which represents the stem loop IIIB of the HCV 5'-UTR, the zinzyme sensor

demonstrates an activity increase of three logs in cleaving the reporter molecule component of the sensor molecule as shown in the graph (+ oligo target) as compared to the sensor molecule in the absence of the target. In the presence of the full length 350 nt. HCV 5'-UTR, the zinzyme sensor molecule demonstrates an almost one log increase in activity in cleaving the reporter molecule component of the sensor molecule.

The paragraph beginning on Page 94, line 27:

Figure 26 shows a non-limiting example of target signaling molecule inactivation of a zinzyme sensor molecule. In the absence of the target (SEQ ID NO. [31]**34**), the zinzyme sensor molecule (SEQ ID NO. [32]**35**) catalyzes the cleavage of a reporter molecule (SEQ ID NO. [33]**36**). Reaction conditions: 140mM KCl, 10mM NaCl, 20 mM HEPES pH 7.4, 1mM MgCl[2]$_2$, 1mM CaCl[2]$_2$, 400 nM Nucleic acid sensor, 400 nM Target, Trace of labeled reporter (~10 nM), 25μl reaction volume, Nucleic acid sensor, target and reporter were heated at 75°C for 3 min, cooled to 37°C and cleavage initiated by the addition of MgCl[2]$_2$ and CaCl[2]$_2$.

The paragraph beginning on Page 95, line 6:

Figure 27 shows a non-limiting example of target signaling molecule activation of a zinzyme sensor molecule. In the presence of the target (SEQ ID NO. [34]**37**), the zinzyme sensor molecule (SEQ ID NO. [35]**38**) catalyzes the cleavage of a reporter molecule (SEQ ID NO. [36]**39**). Reaction conditions: 140mM KCl, 10mM NaCl, 20 mM HEPES pH 7.4, 1mM MgCl[2]$_2$, 1mM CaCl[2]$_2$, 400 nM Nucleic acid sensor, 400 nM Target, Trace of labeled reporter (~10 nM), 25μl reaction volume, Nucleic acid sensor, target and reporter were heated at 75°C for 3 min, cooled to 37°C and cleavage initiated by the addition of MgCl[2]$_2$ and CaCl[2]$_2$.

The paragraph beginning on Page 96, line 12:

An RNA sensor domain that binds to protein ERK2 (Erk) was appended to a variant of the hammerhead enzymatic nucleic acid molecule through a communication module developed through rational design. The salient feature of this design strategy is that substrate-binding elements in the enzymatic nucleic acid molecule domain are

sequestered by complementary allosteric effector sequences present in the communication module in the absence of target. Target association with the sensor domain forces an alternative RNA conformation in which the substrate binding elements become available for interaction with cleavage substrate, thus promotion catalysis. **Figure 28** shows a non-limiting example of a nucleic acid sensor molecule that is modulated by a protein target signaling molecule, Erk. In the presence of the target protein (Erk), the nucleic acid sensor molecule (SEQ ID NO. [39]**41**) catalyzes the cleavage of a reporter molecule. Reaction conditions: 100mM KCl, 1mM MgCl[2]$_2$, 10mM Tris 7.5, 10μM ERK protein, 1μM HH ribozyme, Vf=19μl, 34°C for 30 minutes, trace 5' labeled substrate (1μl)."

The paragraph beginning on Page 99, line 21:

Figure 29 shows a non-limiting example of a "half-zinzyme" nucleic acid sensor molecule with a PEG linker that is modulated by the 5'-UTR of the Hepatitis C virus (HCV 5'-UTR). The figure shows both inactive and active forms of the zinzyme sensor molecule (SEQ ID NO. [42]**43**). In the presence of the target signaling oligonucleotide (SEQ ID NO. [43]**26**) which represents the stem loop IIIB of the HCV 5'-UTR, the zinzyme sensor demonstrates an activity increase of three logs in cleaving the reporter molecule component of the sensor molecule as shown in the graph (+ oligo target) as compared to the sensor molecule in the absence of the target. In the presence of the full length 350 nt. HCV 5'-UTR, the zinzyme sensor molecule demonstrates an almost one log increase in activity in cleaving the reporter molecule component of the sensor molecule. Reaction conditions: 140mM KCl, 10mM NaCl, 20 mM HEPES pH 7.4, 1mM MgCl[2]$_2$, 1mM CaCl[2]$_2$, 400 nM Nucleic acid sensor, 400 nM Target, Trace of labeled reporter (~10 nM), 25μl reaction volume, Nucleic acid sensor, target and reporter were heated at 75°C for 3 min, cooled to 37°C and cleavage initiated by the addition of MgCl[2]$_2$ and CaCl[2]$_2$.